

WHAT IS CLAIMED IS:

1. A method for alleviating stuttering, in a subject in need thereof,  
comprising:

5 administering a therapeutically effective dose of a gamma-aminobutyric acid  
receptor modulator, its pharmaceutically acceptable salts, enantiomers, or metabolites  
thereof.

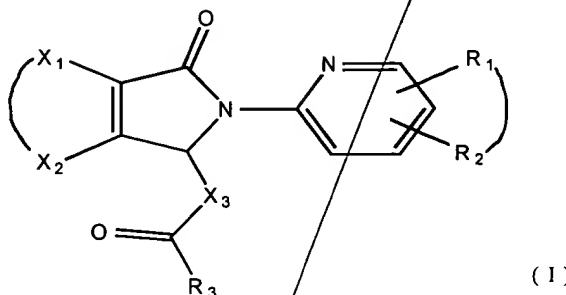
2. The method according to claim 1,

wherein said modulator comprises: allopregnanolone, alphaxalone, alprozolam,  
?? SP?

10 amobarbital, aprobarbital, avermectin B,  $\pm$  baclofen, bicuculline, butabarbital, butalbital,  
camazepam, cloflubicyne, chlordiazepoxide, clorazepam, chlorazepate, diazepam,  
diazepam binding inhibitory protein, diazepam binding inhibitory protein fragment,  
dihydroepiandrosterone, epiallopregnanolone, estazolam, etbicuphat, etbicythionat,  
etomidate, flucybene, flunitrazepam, flurazepam, halazepam, D- $\beta$ -hydrastine,  
15 isobicyphat, lorazepam, mebicyphat, mephobarbital, methohexital, midazolam,  
oxazepam, pagoclone, pentobarbitone, pentobarbital, phenobarbital, picrotoxinin,  
picrotin, pinazepam, prazepam, pregnanolone, pregnenolone, progesterone, propofol,  
propylbicyphat, quazepam, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-  
oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-  
20 acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-  
oxohexyl)-1-isoindolinone, secobarbital, suriclone, tenazepam,  
tetrahydrodeoxycorticosterone, tetramethylene sulfotetramide, thiopental, triazolam,  
zopiclone, pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites  
thereof.

3. The method according to claim 1, wherein the modulator has the formula

(I):



wherein:

- (a)  $R_1$  and  $R_2$  are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen; alkyl having 1 to 8 carbon atoms; alkyl having 1 to 8 carbon atoms, and having at least one of nitrogen, oxygen, sulfur, or phosphorus; aryl having 1 to 8 carbon atoms; and aryl having 1 to 8 carbon atoms and having at least one nitrogen, oxygen, sulfur, or phosphorus;

- (b)  $R_3$  is selected from the group of substituents consisting of: alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the proviso that each of the foregoing  $R_3$  substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms, aryl, alkaryl, piperazinyl, and methyl-piperazinyl;

- (c)  $X_1$  and  $X_2$  are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl

having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing X<sub>1</sub> and X<sub>2</sub> substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms; and

(d) X<sub>3</sub> is selected from the group consisting of: a methylene; —C(HR<sub>4</sub>)— where R<sub>4</sub> is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R<sub>4</sub> substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; amino; —N(R<sub>5</sub>)— where R<sub>5</sub> is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R<sub>5</sub> substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; sulfur; phosphorus; and oxygen group; pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

4. The method according to claim 3, wherein R<sub>1</sub> and R<sub>2</sub> are covalently bonded to form a polycyclic structure.

5. The method according to claim 3, wherein the cycloalkyl of R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>,

and X<sub>2</sub> are the same or different, and each have up to 3 alkyl substituents.

6. The method according to claim 3, wherein the cycloalkenyl of R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> are the same or different, and each have up to 3 alkyl substituents.

7. The method according to claim 3, wherein the cycloalkylalkyl of R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> are the same or different and each have up to 3 alkyl substituents.

8. The method according to claim 3, wherein the cycloalkenylalkyl of R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> are the same or different and each have up to 3 alkyl substituents.

9. The method according to claim 3, wherein X<sub>1</sub> and X<sub>2</sub> are covalently bonded to form a polycyclic structure.

10. The method according to claim 1, additionally comprising a pharmaceutically acceptable carrier.

11. The method according to claim 1, wherein said modulator is effective at the receptor subtype A.

12. The method according to claim 1, wherein said modulator is an agonist of the receptor subtype A.

13. The method according to claim 1, wherein said administration is performed parenterally, orally, vaginally, rectally, nasally, buccally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, transdermally, intracerebroventricularly, or combinations thereof.

14. The method according to claim 1, wherein said modulator comprises a cyclopyrrolone.

15. The method according to claim 1, wherein the dose is about 0.01 to about 1000 mg.

16. The method according to claim 15, wherein the dose is about 0.1 mg to about 10 mg.

17. The method according to claim 2, wherein said modulator comprises pagoclone, suriclone, zopiclone, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, pharmaceutically acceptable salts thereof, enantiomers

thereof, or metabolites thereof.

18. The method according to claim 17, wherein the modulator comprises pagoclonide.

19. The method according to claim 18, wherein the pagoclonide is administered at least once daily.

20. The method according to claim 1, wherein the subject is suffering from stuttering, motor tic, clonic stuttering, dysfluency, speech blockage, dysarthria, Tourette's syndrome, or logospasm.

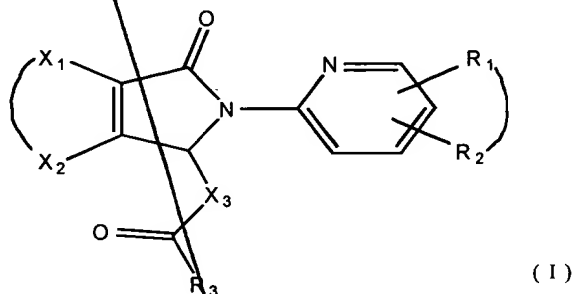
21. A method of alleviating stuttering, in a subject in need thereof, comprising:

administering a therapeutically effective dose of a gamma-amino butyric acid receptor modulator, pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof, and a second active ingredient.

22. A pharmaceutical composition for alleviating stuttering, in a subject in need thereof, comprising:

a therapeutically effective amount of a gamma-aminobutyric acid receptor modulator, its pharmaceutically acceptable salts, enantiomers, metabolites, or combinations thereof, and a second active ingredient.

23. The pharmaceutical composition according to claim 22, wherein said gamma-aminobutyric acid receptor modulator is formula I:



wherein:

(a)  $R_1$  and  $R_2$  are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen; alkyl having 1 to 8 carbon atoms; alkyl having 1 to 8 carbon atoms, and having at least one of nitrogen, oxygen, sulfur, or phosphorus; aryl having 1 to 8 carbon atoms; and aryl having 1 to 8 carbon atoms and having at least one nitrogen, oxygen, sulfur, or phosphorus;

(b)  $R_3$  is selected from the group of substituents consisting of: alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the proviso that each of the foregoing  $R_3$  substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms, aryl, alkaryl, piperazinyl, and methyl-piperazinyl;

(c)  $X_1$  and  $X_2$  are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing  $X_1$  and  $X_2$  substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms; and

(d)  $X_3$  is selected from the group consisting of: a methylene;  $—C(HR_4)—$  where  $R_4$  is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl,

alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl  
having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl  
having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the  
additional proviso that each of the foregoing R<sub>4</sub> substituents has up to 8 carbon atoms,  
5 trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl  
having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms;  
amino; —N(R<sub>5</sub>)— where R<sub>5</sub> is selected from the group of substituents consisting of alkyl,  
alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl,  
alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino,  
10 alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino,  
alkoxycarbonylaminoalkyl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4  
to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having  
4 to 6 ring members, with the additional proviso that each of the foregoing R<sub>5</sub>  
substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen,  
15 aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and  
aminocarbonylalkyl having 2 to 4 carbon atoms; sulfur; phosphorus; and oxygen group;  
pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

24. The composition according to claim 23, wherein R<sub>1</sub> and R<sub>2</sub> are covalently  
bonded to form a polycyclic structure.

20 25. The composition according to claim 23, wherein the cycloalkyl of R<sub>3</sub>, R<sub>4</sub>,  
R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> each have up to 3 alkyl substituents.

26. The composition according to claim 23, wherein the cycloalkenyl of R<sub>3</sub>,  
R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> each have up to 3 alkyl substituents.

27. The composition according to claim 23, wherein the cycloalkylalkyl of R<sub>3</sub>,  
25 R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> each have up to 3 alkyl substituents.

28. The composition according to claim 23, wherein the cycloalkenylalkyl of  
R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, X<sub>1</sub>, and X<sub>2</sub> each have up to 3 alkyl substituents.

29. The composition according to claim 23, wherein X<sub>1</sub> and X<sub>2</sub> are covalently  
bonded to form a polycyclic structure.

30 30. The pharmaceutical composition according to claim 23 wherein formula I

is a cyclop~~yr~~rolone.

31. The pharmaceutical composition according to claim 30, wherein the cyclopyrrolone comprises pagoclone, suriclone, zopiclone, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, pharmaceutically acceptable salts thereof, enantiomers thereof, metabolites thereof, or combinations thereof.

32. The pharmaceutical composition according to claim 30, wherein said cyclopyrrolone comprises pagoclone.

10 33. A method for alleviating stuttering, in a subject in need thereof,  
comprising:

administering a dose of pagoclone in a pharmaceutically acceptable carrier, where the pagoclone is present in an amount between about 0.1 mg and about 10 mg.

**THE UNIVERSITY OF CHICAGO**

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